REMARKS

Upon entry of the Amendment, Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 52-55 are pending in the application. Claims 1-14, 18-20, 23, 25-30, 32-33, 36-41, 44, 46-47, 49-51 and 56 are canceled without prejudice. Claims 15, 21, 24, 42, 48, and 52-55 have been amended. No new matter has been added. Support for the amendments to the claims can be found in the claims and throughout the specification as originally filed, for example, Example 1, and Figures 1-5.

Amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Acknowledgement of the Withdrawal of Previous Rejections

Applicants gratefully acknowledge the withdrawal of the previous rejections of the claims under 35 USC §102(b).

Rejections Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 15-17, 21-24, 31, 34, 35, 42, 43, 45, 48, 52, and 53 under 35 U.S.C. 112, first paragraph, contending that the specification is not enabling for treating arthritis with 0.01- 0.1 mg/kg of any anti-TNFα antibody. Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Not in acquiescence of the rejection but in order to expedite allowance of certain claims, and without prejudice to pursue the canceled or amended claims in this or a continuing application, Applicants have amended claims such that independent claims 15, 21, 42, and 48 recite a fully human anti-TNF antibody. Applicants' claims 15, 21, 42, and 48 no longer encompass Infliximab, which is not a fully human antibody but rather a human/mouse chimeric IgG1. In addition, contrary to the Examiner's apparent contention that a 0.01 mg/kg does of an anti-TNF antibody for treating arthritis is not enabled, Applicants respectfully submit that Figures 1 and 4, for example, indicate that there is a dose dependent decrease in mean arthritic

score compared to control mice, for example, after treatment with a 0.01 mg/kg dose and a 0.1 mg/kg dose of fully human anti-TNF antibody D2E7. Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 103(a)

The Examiner rejected claims 15-17, 21-24, 31, 34, 35, 42, 43, 45, 48, and 52-56 under 35 U.S.C. § 103(a) as being obvious over Stephens *et al.* (Antibody Therapeutic (1997), pp 317-340, eds. Harris *et al.*, CRC: Boca Raton, Fla.) in view of Salfeld et al. (U.S. Patent No. 6,258,562; hereinafter referred to as "Salfeld") and den Broeder *et al.* (Rheumatology 2002, 41(6):638-42; hereinafter "den Broeder"). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

As discussed in Applicants prior response, the Examiner is combining references that describe different dosage forms, different antibodies, and different results (or indeed lack of results) for suggesting Applicants invention. Stephens, as discussed above, does not teach an injection regime for a fully human anti-TNFα antibody as a treatment for arthritis or alleviating its symptoms. Stephens discloses studies using a humanized anti-TNF antibody, which is a mouse-human chimera, which is completely different from a fully human anti-TNF antibody. Applicants submit that dosages of a humanized antibody and of a fully human antibody would not be expected to correlate, such that a skilled artisan would not rely on the teachings of Stephens for any motivation or suggestions regarding dosage or other characteristic of a fully human antibody. Even if, *arguendo*, a skilled artisan could rely on Stephens, Stephens provides no evidence or suggestion that a 0.01 mg/kg dosage would be effective at treating arthritis or alleviating a symptom using a fully human anti-TNF antibody. Since Stephens provides no data that suggests a 0.01 mg/kg dose of even a humanized antibody would treat arthritis or a symptom, a skilled artisan, using Stephens as a guide, would not be motivated to use that dose to treat arthritis. One of ordinary skill in the art would not have been motivated, based on the disclosure of Stephens, to treat arthritis with a low dose of 0.01-0.1 mg/kg, since Stephens provides no evidence that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis and, moreover, teaches that a low dose of an antibody mounts an immune response and is cleared

from the patient's system to a greater extent than a higher dose, *e.g.*, 10 mg/kg, of CDP571. Applicants therefore urge that Stephens teaches away from the claims as amended.

Salfeld fails to make up for this deficiency. Salfeld provides general guidance with regard to normally prescribed dosing but fails to teach or suggest methods that use a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody or a reasonable expectation of success for treating arthritis at those doses. Applicants, on the other hand, came upon this surprising result empirically as described in the Example section of the instant application. On the contrary, as acknowledged by the Examiner, Salfeld teaches that a dose range for human anti-TNFα antibodies is 0.1-20 mg/kg. However, Salfeld disclosed only treatment of rheumatoid arthritis using a range of 1.5 mg/kg to 30 mg/kg (see Example 4, part D, section III, Table 15). Salfeld thus fails to teach or suggest the treatment of arthritis in the 0.01-0.1 mg/kg range. Moreover, one of ordinary skill in the art would not have been motivated to arrive at the claimed invention, *i.e.*, to select the claimed dosage range of 0.01 to 0.1 mg/kg, based on the disclosure of Salfeld, because Salfeld already teaches the successful inhibition of human TNFα activity using a dosage range of 0.1-20 mg/kg. Further, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. §2131.03). In the present case, while the Salfeld discloses a dose range which "touches" the claimed dose range of 0.01-0.1 mg/kg, the unexpected results provided by Applicants, particularly in view of the lack of evidence anywhere else in the prior art, further prove that the pending claims are unobvious over the teachings of Salfeld.

Den Broeder also fails to make up for the deficiencies of Stephens and Salfeld. Den Broeder discloses a much larger dose of 2.5 mg/kg delivered intravenously every 2-4 weeks. At no time does Den Broeder inject less than a 0.25 mg/kg dose, which is well above and outside Applicants' dose range required in the claims as amended.

Den Broeder reports that "six out of 21 patients were placed back on the original dose of 3.0 mg/kg after flaring on 1.0 mg/kg, whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg." Further, den Broeder discloses that, based on these results, the median of the calculated weekly dose of anti-TNFα administered to these patients

was 0.36 mg/kg per week. Thus, den Broeder fails to teach or suggest a method of treating arthritis by administering a dose lower than 0.25 mg/kg, let alone a low dose of 0.01-0.1 mg/kg of an anti-TNFα antibody, as required by the instant claims.

One of skill in the art would not have been motivated, based on the disclosure of den Broeder, to practice the claimed invention of treating arthritis at a low dose of 0.01-0.1 mg/kg because Den Broeder teaches away. Den Broeder teaches that "[a] drawback of step-down dose titration is the inevitable disease flare in the titration phase" and note that "eighteen out of 21 patients experienced a flair of the disease" (page 641, last paragraph; emphasis added). Indeed, only three out of 21 patients reached the dose of 0.25 mg/kg, while the remaining 18 patients experienced a flair in disease at even higher doses. Thus, den Broeder teaches away from the claimed low dose of 0.01-0.1 mg/kg in that it teaches that even at a dose of 0.25 mg/kg (or greater), 18 out of the 21 patients treated experienced a flair in disease. One of ordinary skill in the art would not have been motivated nor have had a reasonable expectation of success, based on the disclosure of den Broeder, to treat with doses lower than 0.25 mg/kg, since only a small percentage of patients (i.e., 3 out of 21) were observed to reach the dose of 0.25 mg/kg before exhibiting a flare in disease.

In view of all of the foregoing, it is evident that Stephens in view of the teachings of Salfeld and den Broeder fail to render the claim as amended obvious. Accordingly, Applicants respectfully request that the rejection of claims under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Provisional Rejection Under the Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 15-17, 21-24, 31, 34, 35, 42, 43, 45, 48, and 52-56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (a) claims 1-7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69, and 70 of US Patent No. 6,509,015; (b) claims 1-10 of US Patent No. 7,223,394 (hereinafter the '394 patent); and (c) claims 17, 41, 79, 86, 103, 110, 115, 122, 127, and 134 of co-pending U.S. Application No. 11/233,252 (hereinafter referred to as "the '252 application"), each in view of Salfeld and den Broeder.

Regarding the '252 application, Applicants respectfully acknowledge the provisional rejection of these claims and request that the rejection be held in abeyance until allowance of the claims at which time an analysis of the double patenting rejection will be conducted to determine the appropriateness of a terminal disclaimer.

Applicants respectfully traverse the aforementioned obviousness-type double patenting rejection over the '015 and '294 patents on the grounds that the claimed low dose methods would not have been obvious to one of ordinary skill in the art based on the claims of the '015 patent or the '394 patent, in view of the above discussion of Salfeld and den Broeder.

A nonstatutory basis exists for a double patenting rejection when the claimed invention is an obvious variation of an invention in an issued patent (M.P.E.P. § 804(B)(1)). Accordingly, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when considering prior art disclosing a range which "touches" the claimed range, "unexpected results [within the claimed narrow range] may... render the claims unobvious" (see M.P.E.P. § 2131.03).

The claimed methods are unique in that they embody Applicants' unexpected discovery that low doses, *e.g.*, 0.01-0.1 mg/kg, of fully human anti-TNFα antibodies can be effective in treating arthritis and alleviating symptoms associated with arthritis. Applicants teach in the specification various benefits associated with administering low doses of the fully human anti-TNFα antibodies, including improvement in cartilage erosion (see, for example, Table 2 at page

29 of the specification). Applicants also teach in the specification that low doses of a fully human anti-TNFα antibody may be advantageous as they may decrease side effects and may decrease the frequency of administration associated with the normally prescribed dose (see, for example, page 7, lines 20-22 of the specification). In contrast, the '015 and '394 patents fail to teach or suggest a low dose of 0.01 – 0.1 mg/kg of a fully human anti-TNFα antibody, either alone or in combination with Salfeld or den Broeder, as discussed above for the rejections under 35 USC 103 (a).

Accordingly, Applicants respectfully request that the rejection of claims under the judicially created doctrine of obviousness-type double patenting be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 102(a)

The Examiner rejected claims 52-56 under 35 U.S.C. § 102(a) as being anticipated by den Broeder *et al.* (Rheumatology 2002, 41(6):638-42; hereinafter "den Broeder"). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Not in acquiescence of the rejection but in order the expedite allowance of the claims Applications have amended claims 52-55 to exclude D2E7. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be reconsidered and withdrawn.

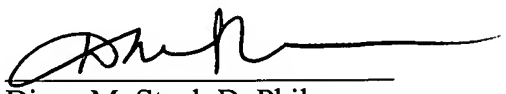
Rejection Under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 52, 53, and 56 under 35 U.S.C. § 102(a) as failing to comply with written description for reciting "enantercept". Applicants respectfully submit that this typographical error has been corrected by substituting "etanercept" for "enantercept". Support for this amendment can be found for example on page 26, line 22. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would help expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (508) 688-8048.

Respectfully submitted,



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